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(54) Title: SULFONAMIDES

(57) Abstract: The present invention relates to sulfonamides, pharmaceutical compositions containing them, and their use as antagonists of urotensin II.

SULFONAMIDES

FIELD OF THE INVENTION

The present invention relates to sulfonamides, pharmaceutical compositions
5 containing them and their use as urotensin II antagonists

BACKGROUND OF THE INVENTION

The integrated control of cardiovascular homeostasis is achieved through a combination of both direct neuronal control and systemic neurohormonal activation.
10 Although the resultant release of both contractile and relaxant factors is normally under stringent regulation, an aberration in this *status quo* can result in cardiohemodynamic dysfunction with pathological consequences.

The principal mammalian vasoactive factors that comprise this neurohumoral axis, namely angiotensin-II, endothelin-1, norepinephrine, all function via an interaction with
15 specific G-protein coupled receptors (GPCR). Urotensin-II, represents a novel member of this neurohumoral axis.

In the fish, this peptide has significant hemodynamic and endocrine actions in diverse end-organ systems and tissues:

- smooth muscle contraction
20 both vascular and non-vascular in origin including smooth muscle preparations from the gastrointestinal tract and genitourinary tract. Both pressor and depressor activity has been described upon systemic administration of exogenous peptide
- osmoregulation:
effects which include the modulation of transepithelial ion (Na^+ , Cl^-) transport.
25 Although a diuretic effect has been described, such an effect is postulated to be secondary to direct renovascular effects (elevated GFR)
- metabolism:
urotensin-II influences prolactin secretion and exhibits a lipolytic effect in fish
(activating triacylglycerol lipase resulting in the mobilization of non-esterified free
30 fatty acids)
(Pearson, *et. al. Proc. Natl. Acad. Sci. (U.S.A.)* 1980, 77, 5021; Conlon, *et. al. J. Exp. Zool.* 1996, 275, 226.)

In studies with human Urotensin-II it was found that it:

- was an extremely potent and efficacious vasoconstrictor
- exhibited sustained contractile activity that was extremely resistant to wash out
- had detrimental effects on cardiac performance (myocardial contractility)

5 Human Urotensin-II was assessed for contractile activity in the rat-isolated aorta and was shown to be the most potent contractile agonist identified to date. Based on the *in vitro* pharmacology and *in vivo* hemodynamic profile of human Urotensin-II it plays a pathological role in cardiovascular diseases characterized by excessive or abnormal vasoconstriction and myocardial dysfunction. (Ames *et. al. Nature* **1999**, *401*, 282; Douglas
10 & Ohlstein (2001). Trends Cardiovasc. Med., 10: in press).

Compounds that antagonize the Urotensin-II receptor may be useful in the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, fibrosis (e.g. pulmonary fibrosis), restenosis, atherosclerosis, dyslipidemia, asthma, (Hay DWP, Luttmann MA,
15 Douglas SA: 2000, Br J Pharmacol: **131**; 10-12) neurogenic inflammation and metabolic vasculopathies all of which are characterized by abnormal vasoconstriction and/or myocardial dysfunction. Urotensin antagonists may provide end organ protection in hypersensitive cohorts in addition to lowering blood pressure.

Since U-II and GPR14 are both expressed within the mammalian CNS (Ames *et. al. Nature* **1999**, *401*, 282), they also may be useful in the treatment of addiction,
20 schizophrenia, cognitive disorders/Alzheimers disease, (Gartlon J. Psychopharmacology (Berl) 2001 June; 155(4):426-33), impulsivity, anxiety, stress, depression, pain, migraine, neuromuscular function, parkinsons, movement disorders, sleep-wake cycle, and incentive motivation (Clark *et al. Brain Research* 923 (2001) 120-127.

25 Functional U-II receptors are expressed in rhabdomyosarcomas cell lines and therefore may have oncological indications. Urotensin may also be implicated in various metabolic diseases such as diabetes (Ames *et. al. Nature* **1999**, *401*, 282, Nothacker et al., *Nature Cell Biology* 1: 383-385, 1999) and in various gastrointestinal disorders, bone, cartilage, and joint disorders (e.g. arthritis and osteoporosis); and genito-urinary disorders.
30 Therefore, these compounds may be useful for the prevention (treatment) of gastric reflux, gastric motility and ulcers, arthritis, osteoporosis and urinary incontinence.

SUMMARY OF THE INVENTION

In one aspect this invention provides for sulfonamides and pharmaceutical
35 compositions containing them.

In a second aspect, this invention provides for the use of sulfonamides as antagonists of urotensin II, and as inhibitors of urotensin II.

In another aspect, this invention provides for the use of sulfonamides for treating conditions associated with urotensin II imbalance.

5 In yet another aspect, this invention provides for the use of sulfonamides for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), renal disease (acute and chronic renal failure/end stage renal disease) along with peripheral vascular disease (male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb
10 disease) and ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis (e.g. pulmonary fibrosis), sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity, anxiety, stress, depression, parkinsons, movement disorders, sleep-wake cycle, incentive
15 motivation, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

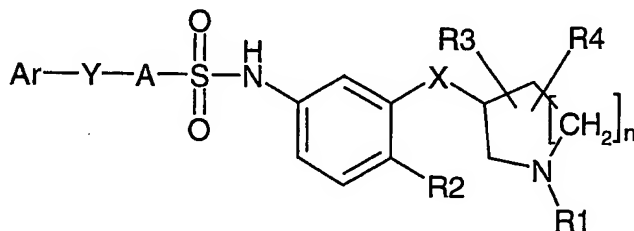
The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, A-II
20 receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β -adrenoceptor and α_1 -adrenoceptor antagonists.

Other aspects and advantages of the present invention are described further in the following detailed description of the preferred embodiments thereof.

25

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for compounds of Formula (I):



Formula (I)

30

wherein:

- Ar is phenyl, pyridinyl, thienyl, furanyl, oxazolyl, pyrrolyl, triazinyl, imidazolyl, pyrimidinyl, pyrazinyl, oxadiazolyl, pyrazolyl, triazolyl, thiazolyl, thiadiazolyl, quinolinyl, naphthyridinyl, benzodioxanyl, benzodioxolyl, benzodioxepinyl, azaspirotonoyl, substituted or unsubstituted
- 5 by one, two, three or four of the following: halogen, CN, S(C₁₋₆ alkyl), CF₃, OCF₃, SCF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, CO₂(C₁₋₆ alkyl), NR₅R₆, CONR₇R₈, or NO₂;
- A is phenyl, thienyl, furanyl, pyridinyl, oxazolyl, pyrrolyl, triazinyl, imidazolyl, pyrimidinyl, pyrazinyl, N-phenylpyrrolyl, oxadiazolyl, pyrazolyl, triazolyl, thiazolyl, thiadiazolyl, naphthyl, indoyl, quinolinyl, quinazolinyl, naphthyridinyl, benzothiophenyl, benzofuranyl,
- 10 benzodioxanyl, benzodioxolyl, benzodioxepinyl, benzothiazolyl, benzoxazolyl, benzothiadiazolyl, benzoxadiazolyl, or benzimidazolyl, all of which may be substituted or unsubstituted by one, two, three or four halogens, C₁₋₆ alkyl, C₁₋₆ alkoxy, CO₂(C₁₋₆ alkyl), CN, or CF₃ groups;
- Y is O, NH, -C(O)-NH-CH₂-, -S(O_n)-, CH₂, or a bond;
- 15 R₂ is hydrogen, halogen, CF₃, CN, or C₁₋₄ alkyl;
- R₁, R₃, R₄, R₅, R₆, R₇, and R₈ are independently hydrogen, C₁₋₆ alkyl, or benzyl;
- X is O, S, or CH₂;
- n is 0, 1, or 2;
- or a pharmaceutically acceptable salt thereof.

20

When used herein, the term "alkyl" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

25 When used herein, the terms 'halogen' and 'halo' include fluorine, chlorine, bromine and iodine and fluoro, chloro, bromo and iodo, respectively.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and their diastereoisomers are contemplated to be within the scope of the present invention.

30 Preferably Ar is phenyl, pyridinyl, naphthyridinyl, or azaspirotonoyl substituted or unsubstituted by one, two, three or four of the following: halogen, CN, or CF₃.

Preferably A is phenyl, pyrrolyl, N-phenylpyrrole, or furanyl substituted or unsubstituted by halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, or CO₂(C₁₋₆ alkyl).

Preferably Y is O or a bond.

Preferably R₁ is C₁₋₆ alkyl.

Preferably R₂ is halogen.

Preferably R₃ is hydrogen.

5 Preferably R₄ is hydrogen.

Preferably X is O.

Preferably n is 1.

Preferred Compounds are:

- 10 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[3-(2-chlorophenoxy)]benzenesulfonamide;
(±)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(2-cyano-3-chlorophenoxy)]benzene-sulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(2-cyano-3-chlorophenoxy)]benzene-sulfonamide;
- 15 (S)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(2-cyano-3-chlorophenoxy)]benzene-sulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(4-trifluoromethyl-6-chloro-2-pyridinyloxy)] benzenesulfonamide;
- 20 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-[(5,7-ditrifluoromethyl)[1,8]naphthyridine-2-oxy]-benzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(3,5-dichlorophenoxy)]benzene-sulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2-chloro-4-(2-cyano-3-chlorophenoxy)] benzenesulfonamide;
- 25 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2-methyl-4-(2-cyano-3-chlorophenoxy)] benzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-1-(4-trifluoromethyl-6-chloro-2-pyridyl)-pyrrole-2-sulfonamide;
- 30 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3-chloro-4-[1-(2-azaspiro[4.4]nonanoyl)]-benzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-1-(2,5-dimethyl-4-ethoxycarbonyl)-phenylpyrrole-3-sulfonamide;

- (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-1-[2-methyl-4-ethoxycarbonyl-5-(4-chlorophenyl)]-phenylpyrrole-3-sulfonamide;
- (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-1-(2-methyl-4-ethoxycarbonyl-5-phenyl)-phenylpyrrole-3-sulfonamide;
- 5 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2-(4-chlorophenyl)-4-ethoxycarbonyl-5-methyl-furan-3-sulfonamide];
- (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(3-chlorophenoxy)] benzene-sulfonamide;
- (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2,6-dimethyl-4-(2-cyano-10 3-chloro-phenoxy)] benzenesulfonamide;
- 4-(3-Chloro-2-cyano-phenoxy)-N-(((R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl)-benzenesulfonamide;
- 4-(3,5-Dichlorophenyloxy)-N-(((R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl)-benzenesulfonamide;
- 15 5-Pyridin-2-yl-thiophene-2-sulfonic acid [((R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl]-amide;
- 5-(4-Cyano-1-methyl-5-methylsulfanyl-1-H-pyrazol-3-yl)-thiophene-2-sulfonic acid [((R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl]-amide;
- 5-(5-Trifluoromethyl-isoxazol-3-yl)-thiophene-2-sulfonic acid [((R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl]-amide;
- 20 5-Isoxazol-3-yl-thiophene-2-sulfonic acid [((R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl]-amide; and
- 4-(Chloro-cyano-phenoxy)-2-methyl-N-(((R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl)-benzenesulfonamide.

25

More preferred compounds are:

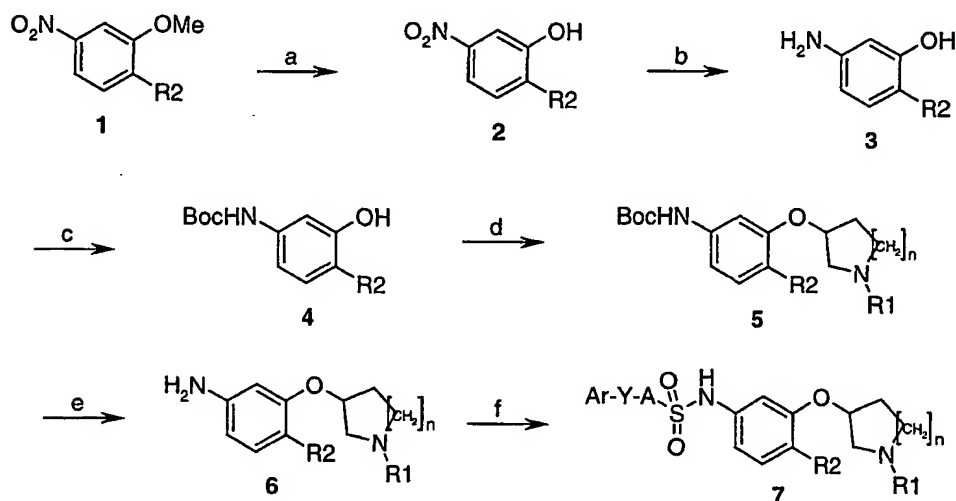
- (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(2-cyano-3-chlorophenoxy)] benzene-sulfonamide;
- (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(3,5-dichlorophenoxy)] benzene-sulfonamide;
- 30 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2,6-dimethyl-4-(2-cyano-3-chloro-phenoxy)] benzenesulfonamide;
- (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2-chloro-4-(2-cyano-3-chlorophenoxy)] benzenesulfonamide;

- 4-(3-Chloro-2-cyano-phenoxy)-N-[(R)-1-methyl-pyrrolidin-3-yloxy]-trifluoromethyl-phenyl]-benzenesulfonamide;
 4-(3,5-Dichlorophenoxy)-N-[(R)-1-methyl-pyrrolidin-3-yloxy]-trifluoromethyl-phenyl]-benzenesulfonamide; or
 5 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2-methyl-4-(2-cyano-3-chloro-phenoxy)] benzenesulfonamide.

Compounds of Formula (I) may be prepared as outlined in Schemes 1 and 2.

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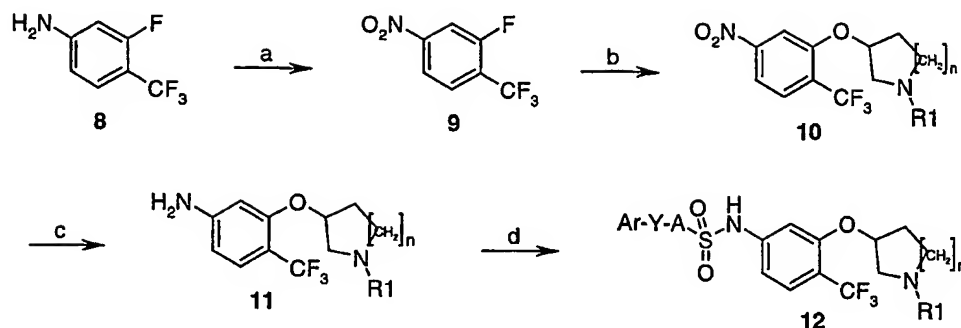
Scheme 1



- Conditions: a) 48% hydrogen bromide, acetic acid; b) hydrogen (50 psi), platinum on carbon, ethyl acetate; c) di-*tert*-butyldicarbonate, tetrahydrofuran, reflux; d) 1-R1-
 15 pyrrolidin-3-ol, DIAD, triphenylphosphine, tetrahydrofuran, 0 °C to room temperature; e) 6 N HCl in dioxane; f) Ar-Y-A-SO₂Cl, chloroform, room temperature.

- For example, acid-mediated demethylation of anisoles **1** gave phenols **2**.
 Hydrogenation of the nitro group provided anilines **3**, which were subsequently protected as
 20 their *tert*-butoxycarbonyl carbamates **4**. Alkylation of **4** with various alcohols using
 standard Mitsunobu conditions, followed by removal of the nitrogen protecting group
 afforded anilines **6**. Subsequent sulfonylation of the anilines furnished the target
 compounds **7**.

Scheme 2



Conditions: a) 50% hydrogen peroxide, trifluoroacetic acid, reflux; b) 1-R1-

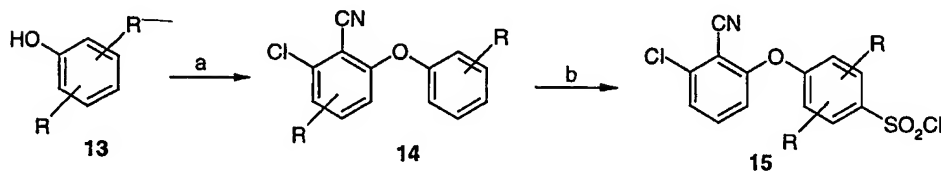
- pyrrolidin-3-ol, sodium hydride, tetrahydrofuran, 0°C; c) hydrogen (50 psi), platinum on carbon, ethyl acetate; d) Ar-Y-A-SO₂Cl, chloroform, room temperature.

For example, oxidation of aniline 8 gave nitrobenzene 9. Substitution of the aryl fluoride with various alcohols furnished the ethers 10. Hydrogenation of the nitro group provided anilines 11, which were subsequently sulfonated with various sulfonyl chlorides to furnish the target compounds 12.

With appropriate manipulation, including the use of alternative nitrogen protecting group(s), the synthesis of the remaining compounds of Formula (I) was accomplished by methods analogous to those above and to those described in the Experimental section.

A number of sulfonyl chlorides used in the synthesis of the title compounds were not available commercially and may be prepared as follows:

Scheme 3



Conditions: a) Sodium hydride, dimethylsulfoxide; then 2,6-dichlorobenzonitrile, 100 °C; b) chlorosulfonic acid, dichloromethane, 0 °C to ambient temperature.

For example, various phenols **13** were alkylated with 2,6-dichlorobenzonitrile to provide ethers **14**. Treatment of **14** with chlorosulfonic acid furnished the desired sulfonyl chlorides **15**.

5 In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example
10 orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt
15 in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a
20 capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

25 Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or
30 emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-
35 butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or
5 metered aerosol dose, so that the patient may administer to themselves a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for
10 intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof
15 calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient
20 to exhibit the desired activity.

These sulphonamide analogs may be used for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), renal disease (acute and chronic renal failure/end stage renal disease) along with peripheral vascular disease (male erectile dysfunction,
25 diabetic retinopathy, intermittent claudication/ischemic limb disease) and ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis (e.g. pulmonary fibrosis), sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity,
30 anxiety, stress, depression, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, A-II

receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β -adrenoceptor and α_1 -adrenoceptor antagonists.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

- 5 The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

Radioligand binding:

- HEK-293 cell membranes containing stable cloned human and rat GPR-14 (20 ug/assay) were incubated with 200 pM [125 I] h-U-II (200 Ci/mmol⁻¹ in the presence of increasing concentrations of test compounds in DMSO (0.1 nM to 10 uM), in a final incubation volume of 200 ul (20 mM Tris-HCl, 5 mM MgCl₂). Incubation was done for 30 minutes at room temperature followed by filtration GF/B filters with Brandel cell harvester. 125 I labeled U-II binding was quantitated by gamma counting. Nonspecific binding was defined by 125 I U-II binding in the presence of 100 nM of unlabeled human U-II. Analysis of the data was performed by nonlinear least square fitting.
- 10
15

Ca²⁺-mobilization:

- A microtitre plate based Ca²⁺-mobilization FLIPR assay (Molecular Devices, Sunnyvale, CA) was used for the functional identification of the ligand activating HEK-293 cells expressing (stable) recombinant GPR-14. The day following transfection, cells were plated in a poly-D-lysine coated 96 well black/clear plates. After 18-24 hours the media was aspirated and Fluo 3AM-loaded cells were exposed to various concentrations (10 nM to 30 uM) of test compounds followed by h-U-II. After initiation of the assay, fluorescence was read every second for one minute and then every 3 seconds for the following one minute. The inhibitory concentration at 50% (IC₅₀) was calculated for various test compounds.
- 20
25

Inositol phosphates assays:

- HEK-293-GPR14 cells in T150 flask were prelabeled overnight with 1 uCi myo-[3 H] inositol per ml of inositol free Dulbecco's modified Eagle's medium. After labeling, the cells were washed twice with Dulbecco's phosphate-buffered saline (DPBS) and then incubated in DPBS containing 10 mM LiCl for 10 min at 37°C. The experiment was initiated by the addition of increasing concentrations of h-U-II (1 pM to 1 μ M) in the absence and presence of three different concentrations (0.3, 1 and 10 uM) of test compounds and the incubation continued for an additional 5 min at 37°C after which the reaction was terminated by the addition of 10% (final concentration) trichloroacetic acid and centrifugation. The supernatants were neutralized with 100ul of 1M Trizma base and the
- 30

inositol phosphates were separated on AG 1-X8 columns (0.8 ml packed, 100-200 mesh) in formate phase. Inositol monophosphate was eluted with 8 ml of 200 mM ammonium formate. Combined inositol di and tris phosphate was eluted with 4ml of 1M ammonium formate/ 0.1 M formic acid. Eluted fractions were counted in beta scintillation counter.

- 5 Based on shift from the control curve K_B was calculated.

Activity for the compounds of this invention range from (radioligand binding assay): $K_i = 10 \text{ nM} - 10000 \text{ nM}$ (example 10 $K_i = 300 \text{ nM}$).

- 10 The following Examples are illustrative but not limiting embodiments of the present invention.

Example 1

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[3-(2-chlorophenoxy)]benzenesulfonamide

15

a). 2-Chloro-5-nitrophenol

- 2-Chloro-5-nitroanisole (310 g, 1.7 mol) was taken up in a mixture of 48% HBr (1.5 L) and AcOH (1.2 L) and heated at reflux for 3 days. The dark solution was allowed to cool to room temperature, poured into ice water (10 L), and let stand for 3 h. The resultant dull
20 yellow solid was filtered, washed with water, and dried in vacuo (230 g, 79%): mp 115-117 °C.

b). 2-Chloro-5-aminophenol

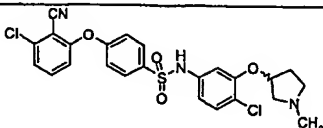
- A solution of 2-chloro-5-nitrophenol (25 g, 0.14 mol) in ethyl acetate (150 mL) was treated
25 with 5% Pt/C (250mg) and the mixture shaken under a hydrogen atmosphere (30 psi) for 4h. The mixture was filtered through Celite® and the residue washed well with hot ethyl acetate. The filtrate was treated with activated charcoal and re-filtered as above. Evaporation of the ethyl acetate gave a solid (19.8 g, 98%).

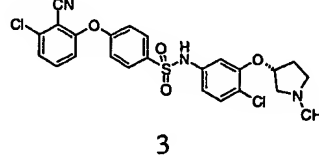
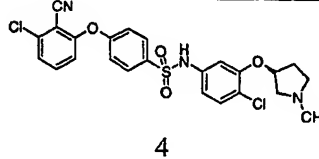
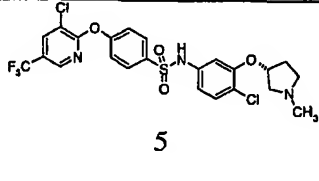
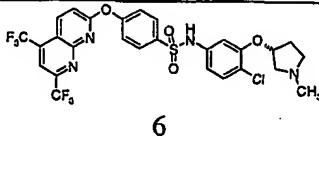
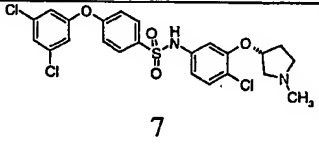
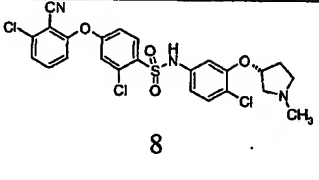
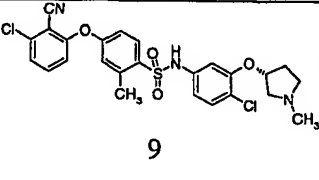
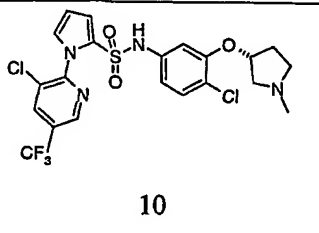
30 c). 4-Chloro-3-hydroxyphenylcarbamic acid tert-butyl ester

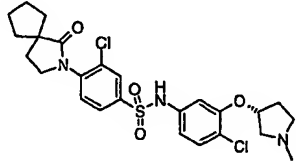
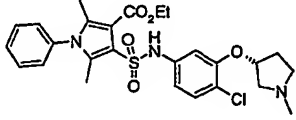
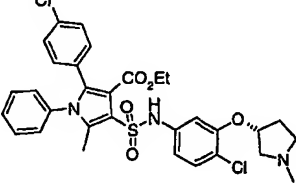
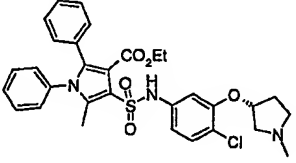
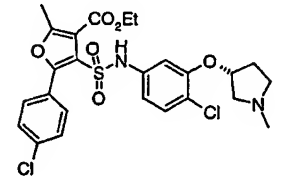
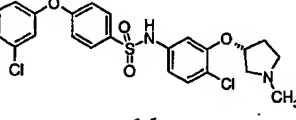
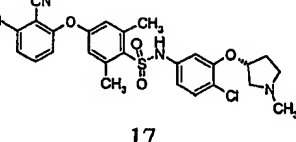
- To a solution of 2-chloro-5-aminophenol (20 g, 0.14 mol) in THF (150 mL) was added a solution of di-tert-butyl dicarbonate (33 g, 0.15 mol) in THF (150 mL). The reaction was heated at reflux for 6 h, at which time it was allowed to cool to room temperature. The solvent was removed *in vacuo* and the residue diluted with ether (500 mL) and washed with
35 1 M citric acid (2 x 300 mL). The aqueous washings were extracted with ether (300 mL)

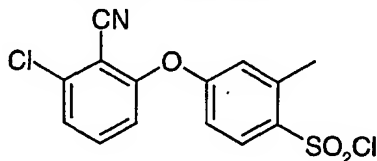
and the combined organics washed with brine (300 mL), dried (MgSO₄), and concentrated. The resultant brown solid was triturated with hexanes and dried in vacuo to give 33 g (97%) of the title compound: mp 103-106 °C.

- 5 d) (R)-[3-(1-Methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-carbamic acid
2-Chloro-5-(*tert*-butoxycarbonyl)phenol (1.9g, 8.0 mmol) was dissolved in tetrahydrofuran (50 mL) and cooled to 0 °C. (R)-3-Methyl-pyrrolidinol (1.05 eq, 8.4 mmol, 0.89g) was added, followed by DIAD (1.5 eq, 13.2 mmol, 2.7g) and triphenylphosphine (1.5 eq, 13.2 eq, 3.4g). The reaction was allowed to warm to room temperature, stirring
10 overnight. The solvent was removed and the residue purified via column chromatography (Flashmaster, 50g silica column, 3-15% isopropanol/chloroform over 40 minutes) to afford the product (1.6g, 60%) as a brown oil.
- e) (R)-3-(1-Methyl-3-pyrrolidinyl)-4-chloroaniline
- 15 (R)-[3-(1-Methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-carbamic acid (1.6g, 4.8 mmol) was taken up in 6N HCl in dioxane (20 mL). After stirring at room temperature for 2 hours, the solvent was evaporated. The residue was basified with 2.5N KOH and extracted 3 x CHCl₃. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to furnish the product (1.1g, 100%) as a dark brown solid.
- 20 f) (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinylloxy)-phenyl]-[3-(2-chloro-phenoxy)]benzenesulfonamide
(R)-3-(1-Methyl-3-pyrrolidinyl)-4-chloroaniline (0.023g, 0.1 mmol) was dissolved in chloroform (35 mL). 3-(2-Chlorophenoxy)benzenesulfonyl chloride (1 eq, 0.1 mmol,
25 0.022g) was added and the mixture was allowed to stir at room temperature overnight. It was concentrated and purified via Gilson HPLC (10-90% acetonitrile/H₂O + 0.1% TFA over 10 minutes) to provide the pure product (0.023g, 47%).

Example	Compound	MS (ES+) m/e [M+H] ⁺
 <p>2</p>	(±)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinylloxy)-phenyl]-[4-(2-cyano-3-chlorophenoxy)] benzene-sulfonamide	518

 <p>3</p>	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(2-cyano-3-chlorophenoxy)] benzene-sulfonamide	518
 <p>4</p>	(S)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(2-cyano-3-chlorophenoxy)] benzene-sulfonamide	518
 <p>5</p>	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(4-trifluoromethyl-6-chloro-2-pyridinyloxy)] benzenesulfonamide	562
 <p>6</p>	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-[(5,7-ditrifluoromethyl)[1,8]naphthyridine-2-oxy]-benzenesulfonamide	647
 <p>7</p>	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(3,5-dichlorophenoxy)] benzene-sulfonamide	527
 <p>8</p>	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2-chloro-4-(2-cyano-3-chlorophenoxy)] benzenesulfonamide	552
 <p>9</p>	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2-methyl-4-(2-cyano-3-chloro-phenoxy)] benzenesulfonamide	532
 <p>10</p>	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-1-(4-trifluoromethyl-6-chloro-2-pyridyl)-pyrrole-2-sulfonamide	535

 <p>11</p>	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3-chloro-4-[1-(2-azaspiro[4.4]nonanoyl)]-benzenesulfonamide	538
 <p>12</p>	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-1-(2,5-dimethyl-4-ethoxycarbonyl)-phenylpyrrole-3-sulfonamide	532
 <p>13</p>	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-1-[2-methyl-4-ethoxycarbonyl-5-(4-chlorophenyl)]-phenylpyrrole-3-sulfonamide	628
 <p>14</p>	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-1-(2-methyl-4-ethoxycarbonyl-5-phenyl)-phenylpyrrole-3-sulfonamide	594
 <p>15</p>	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2-(4-chlorophenyl)-4-ethoxycarbonyl-5-methyl]-furan-3-sulfonamide	553
 <p>16</p>	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(3-chlorophenoxy)] benzene-sulfonamide	493
 <p>17</p>	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2,6-dimethyl-4-(2-cyano-3-chloro-phenoxy)] benzenesulfonamide	546

Example 9a4-(3-Chloro-2-cyano-phenoxy)-2-methyl-benzenesulfonyl chloride

5

a) 2-Chloro-6-*m*-toloxybenzonitrile

To a suspension of sodium hydride (60% in oil, 550 mg, 14 mmol) in DMSO (15 mL) was added a solution of *m*-cresol (1.5 g, 14 mmol) in DMSO (15 mL). The reaction was stirred at ambient temperature for 15 minutes, at which time was added a solution of 2,6-dichlorobenzonitrile (2.3 g, 13 mmol) in DMSO (75 mL). The reaction was heated at 100 °C for 20 hours, allowed to cool to ambient temperature, and poured into water (500 mL). The resultant mixture was extracted with ethyl acetate (2 x 200 mL) and the combined extracts washed with 10% sodium hydroxide (300 mL) and water (300 mL), dried over magnesium sulfate, and concentrated to give 2-chloro-6-*m*-toloxybenzonitrile (2.4 g, 71%).

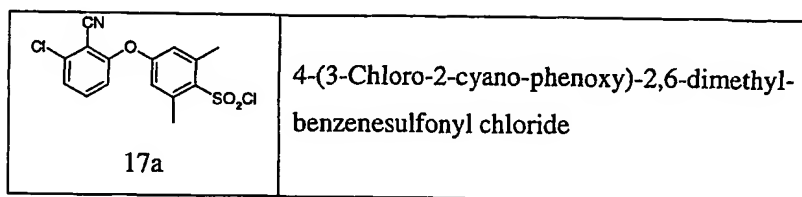
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b) 4-(3-Chloro-2-cyano-phenoxy)-2-methyl-benzenesulfonyl chloride

To a cooled (0 °C) solution of 2-chloro-6-*m*-toloxybenzonitrile (1.1 g, 4.6 mmol) in dichloromethane (25 mL) was added dropwise chlorosulfonic acid (0.46 mL, 7.0 mmol). The reaction was allowed to slowly warm to ambient temperature and maintained for 4 hours, at which time it was concentrated and diluted with ether (30 mL). The resultant solution was then washed with ice cold water (25 mL) and brine (25 mL), dried over magnesium sulfate, and concentrated to furnish a pale yellow oil (690 mg, 43%) which solidified upon standing.

25

Example	Compound
 8a	4-(3-Chloro-2-cyano-phenoxy)-2-chloro-benzenesulfonyl chloride



Examples 18-24

a) 2-Fluoro-4-nitrobenzotrifluoride

- 5 A solution of 4-amino-2-fluorobenzotrifluoride (25.0g, 0.14mol, 1.0eq) in trifluoroacetic acid (140ml) was heated to reflux then was treated with the dropwise addition of 50% hydrogen peroxide (66.7ml, 1.18mol, 8.4eq) over 35min. The reaction was heated at reflux for 1.5hrs further then cooled to ambient temperature. Poured into ice-water (1L) then stirred overnight. The oil that separated was
- 10 collected (decanting the water phase) then diluted with diethyl ether (150ml). The ether solution was washed with aqueous 10% HCl (100ml), saturated aqueous sodium bicarbonate (2x100ml), and brine (100ml) then dried over anhydrous magnesium sulphate. Evaporation under reduced pressure gave an orange-brown oil. Distillation (14torr, 88-90°C) gave the product as a yellow liquid (15.0g, 51%)

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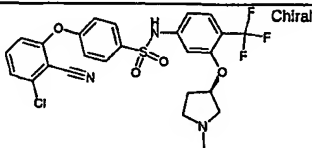
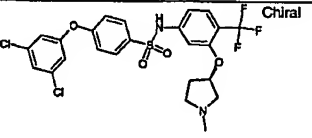
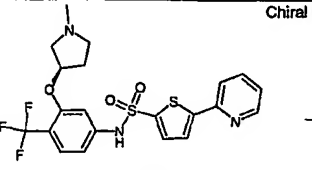
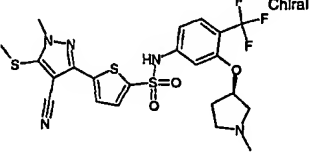
b) (R)-1-Methyl-3-(3-nitro-6-trifluoromethylphenoxy)-pyrrolidine

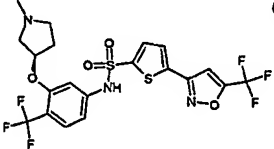
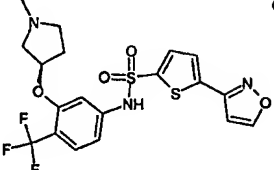
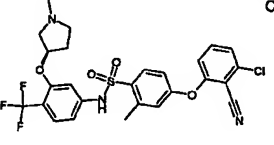
- A solution of 2-fluoro-4-nitrobenzotrifluoride (12.4g, 59.3mmol, 1.0eq) and (R)-1-methyl-pyrrolidin-3-ol (6.0g, 59.3mmol, 1.0eq) in anhydrous tetrahydrofuran (150ml) was cooled to 0°C then slowly treated with portions of 60% sodium hydride
- 20 (4.7g, 0.12mol, 2eq) over 5min. Without removing the ice bath, the reaction was allowed to come to room temperature and stir for 48hrs. Quenched with water (50ml) and brine (100ml) then extracted into diethyl ether (5x100ml). Extracts dried over anhydrous magnesium sulfate and decolorizing charcoal for 1hr. Filtered through Celite. The filtrate was treated with silica (35g) then evaporated to give the
- 25 crude product suspended on silica. Column chromatography on silica (1% MeOH/EtOAc→5%MeOH/EtOAc) gave the product ($R_f \approx 0.3$ in 1%MeOH/EtOAc) as an orange oil (7.85g, 46%).

c) 3-((R)-1-Methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenylamine

A solution of (R)-1-methyl-3-(3-nitro-6-trifluoromethylphenoxy)-pyrrolidine (7.8g, 26.9mmol) in ethyl acetate (50ml) was treated with 10% platinum on carbon (200mg) then subjected to 40psi hydrogen pressure for 3hrs. The slurry was treated with anhydrous magnesium sulfate (5g) then filtered through a pad of Celite. The filter cake was rinsed with ethyl acetate (2x25ml) then the filtrate was evaporated under reduced pressure to an oil. This oil was evaporated twice for dichloromethane (50ml) to remove trapped ethyl acetate. This gave the product as a clear light brown oil that solidified on standing (6.9g, 99%): LCMS 249 ($M^+ + H$).

- 10 Substituting 3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenylamine for (R)-3-(1-methyl-3-pyrrolidinyl)-4-chloroaniline and substituting various sulfonyl chlorides for 3-(2-Chlorophenoxy)benzenesulfonyl chloride, examples 18-24 were prepared following the procedure described in 1f:

Example	Compound	MS (ES+) m/e $[M+H]^+$
 18	4-(Chloro-cyano-phenoxy)-N-(((R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl)-benzenesulfonamide	552
 19	4-Dichlorophenoxy-N-(((R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl)-benzenesulfonamide	561
 20	5-Pyridin-2-yl-thiophene-2-sulfonic acid [((R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl]-amide	484
 21	5-(4-Cyano-1-methyl-5-methylsulfanyl-1-H-pyrazol-3-yl)-thiophene-2-sulfonic acid [((R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl]-amide	558

 22	Chiral 5-(5-Trifluoromethyl-isoxazol-3-yl)-thiophene-2-sulfonic acid [((R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl]-amide	542
 23	Chiral 5-Isoxazol-3-yl-thiophene-2-sulfonic acid [((R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl]-amide	474
 24	Chiral 4-(Chloro-cyano-phenoxy)-2-methyl-N-((R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl]-benzenesulfonamide	566

EXAMPLE 25

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

<u>Tablets/Ingredients</u>	<u>Per Tablet</u>
1.Active ingredient (Cpd of Form. I)	40 mg
2.Corn Starch	20 mg
3.Alginic acid	20 mg
4.Sodium Alginate	20 mg
5.Mg stearate	<u>1.3 mg</u>
	2.3 mg

Procedure for tablets:

Step 1: Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2: Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

- Step 3: The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.
- Step 4: The wet granules are then dried in an oven at 140°F (60°C) until dry.
- Step 5: The dry granules are lubricated with ingredient No. 5.
- 5 Step 6: The lubricated granules are compressed on a suitable tablet press.

Inhalant Formulation

A compound of Formula I, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

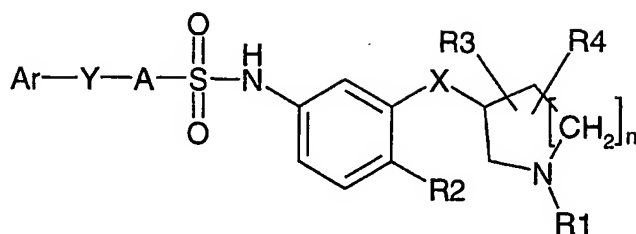
10 Parenteral Formulation

- A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in
- 15 sterile containers.

- The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other
- 20 publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound of Formula (I):



Formula (I)

wherein:

- Ar is phenyl, pyridinyl, thienyl, furanyl, oxazolyl, pyrrolyl, triazinyl, imidazolyl, pyrimidinyl, pyrazinyl, oxadiazolyl, pyrazolyl, triazolyl, thiazolyl, thiadiazolyl, quinolinyl, naphthyridinyl, benzodioxanyl, benzodioxolyl, benzodioxepinyl, azaspirotononyl, substituted or unsubstituted by one, two, three or four of the following: halogen, CN, S(C₁₋₆ alkyl), CF₃, OCF₃, SCF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, CO₂(C₁₋₆ alkyl), NR₅R₆, CONR₇R₈, or NO₂;
- A is phenyl, thienyl, furanyl, pyridinyl, oxazolyl, pyrrolyl, triazinyl, imidazolyl, pyrimidinyl, pyrazinyl, N-phenylpyrrolyl, oxadiazolyl, pyrazolyl, triazolyl, thiazolyl, thiadiazolyl, naphthyl, indolyl, quinolinyl, quinazolinyl, naphthyridinyl, benzothiophenyl, benzofuranyl, benzodioxanyl, benzodioxolyl, benzodioxepinyl, benzothiazolyl, benzoxazolyl, benzothiadiazolyl, benzoxadiazolyl, or benzimidazolyl, all of which may be substituted or unsubstituted by one, two, three or four halogens, C₁₋₆ alkyl, C₁₋₆ alkoxy, CO₂(C₁₋₆ alkyl), CN, or CF₃ groups;
- Y is O, NH, -C(O)-NH-CH₂-, -S(O_n)-, CH₂, or a bond;
- R₂ is hydrogen, halogen, CF₃, CN, or C₁₋₄ alkyl;
- R₁, R₃, R₄, R₅, R₆, R₇, and R₈ are independently hydrogen, C₁₋₆ alkyl, or benzyl;
- X is O, S, or CH₂;
- n is 0, 1, or 2;
- or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein Ar is phenyl, pyridinyl, naphthyridinyl, or azaspirotononyl substituted or unsubstituted by one, two, three or four of

the following: halogen, CN, or CF₃; A is phenyl, pyrrolyl, N-phenylpyrrole, or furanyl substituted or unsubstituted by halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, or CO₂(C₁₋₆ alkyl); Y is O or a bond; R₁ is C₁₋₆ alkyl; R₂ is halogen; R₃ is hydrogen; R₄ is hydrogen; X is O; n is 1.

5 3. A compound according to claim 1 wherein Ar is phenyl which may be substituted or unsubstituted by halogen, CN, SMe, YCF₃, C₁₋₄ alkyl or NO₂; A is phenyl substituted or unsubstituted by halogen or methyl; R₂ is halogen; R₃ is methyl or ethyl; R₄ is methyl or ethyl; R₅ and R₆ are hydrogen; X is O; and Y is an O or a bond.

10 4. A compound according to claim 1 chosen from the group consisting of:
 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[3-(2-chlorophenoxy)]benzenesulfonamide;
 (±)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(2-cyano-3-chlorophenoxy)]
 benzene-sulfonamide;
 15 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(2-cyano-3-chlorophenoxy)]
 benzene-sulfonamide;
 (S)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(2-cyano-3-chlorophenoxy)]
 benzene-sulfonamide;
 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(4-trifluoromethyl-6-chloro-2-
 20 pyridinyloxy)] benzenesulfonamide;
 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-[(5,7-ditri-
 fluoromethyl)[1,8]naphthyridine-2-oxy]-benzenesulfonamide;
 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(3,5-dichlorophenoxy)]
 benzene-sulfonamide;
 25 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2-chloro-4-(2-cyano-3-
 chlorophenoxy)] benzenesulfonamide;
 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2-methyl-4-(2-cyano-3-chloro-
 phenoxy)] benzenesulfonamide;
 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-1-(4-trifluoromethyl-6-chloro-2-
 30 pyridyl)-pyrrole-2-sulfonamide;
 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3-chloro-4-[1-(2-
 azaspiro[4.4]nonanoyl)]-benzenesulfonamide;
 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-1-(2,5-dimethyl-4-
 ethoxycarbonyl)-phenylpyrrole-3-sulfonamide;

- (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-1-[2-methyl-4-ethoxycarbonyl-5-(4-chlorophenyl)]-phenylpyrrole-3-sulfonamide;
- (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-1-(2-methyl-4-ethoxycarbonyl-5-phenyl)-phenylpyrrole-3-sulfonamide;
- 5 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2-(4-chlorophenyl)-4-ethoxycarbonyl-5-methyl]-furan-3-sulfonamide;
- (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(3-chlorophenoxy)] benzene-sulfonamide;
- (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2,6-dimethyl-4-(2-cyano-10 3-chloro-phenoxy)] benzenesulfonamide;
- 4-(Chloro-cyano-phenoxy)-N-[(R)-1-methyl-pyrrolidin-3-yloxy]-trifluoromethyl-phenyl]-benzenesulfonamide;
- 4-Dichlorophenyloxy-N-[(R)-1-methyl-pyrrolidin-3-yloxy]-trifluoromethyl-phenyl]-benzenesulfonamide;
- 15 5-Pyridin-2-yl-thiophene-2-sulfonic acid [(R)-1-methyl-pyrrolidin-3-yloxy]-trifluoromethyl-phenyl]-amide;
- 5-(4-Cyano-1-methyl-5-methylsulfanyl-1-H-pyrazol-3-yl)-thiophene-2-sulfonic acid [(R)-1-methyl-pyrrolidin-3-yloxy]-trifluoromethyl-phenyl]-amide;
- 5-(5-Trifluoromethyl-isoxazol-3-yl)-thiophene-2-sulfonic acid [(R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl]-amide;
- 20 5-Isioxazol-3-yl-thiophene-2-sulfonic acid [(R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl]-amide; or
- 4-(Chloro-cyano-phenoxy)-2-methyl-N-[(R)-1-methyl-pyrrolidin-3-yloxy)-trifluoromethyl-phenyl]-benzenesulfonamide.

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5. A compound according to claim 1 chosen from the group consisting of:

- (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(2-cyano-3-chlorophenoxy)] benzene-sulfonamide;
- (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[4-(3,5-dichlorophenoxy)] benzene-sulfonamide;
- 30 (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2,6-dimethyl-4-(2-cyano-3-chloro-phenoxy)] benzenesulfonamide;
- (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2-chloro-4-(2-cyano-3-chlorophenoxy)] benzenesulfonamide; or

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-[2-methyl-4-(2-cyano-3-chloro-phenoxy)] benzenesulfonamide.

5 6. A pharmaceutical composition comprising a compound of formula (I) of claim 1 and a pharmaceutically acceptable carrier or excipient.

7. A method of treating conditions associated with Urotensin-II imbalance by antagonizing the Urotensin-II receptor which comprises administering to a patient in need thereof, a compound of Formula I of claim 1.

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8. A method according to Claim 7 wherein the disease is congestive heart failure, stroke, ischemic heart disease, angina, myocardial ischemia, cardiac arrhythmia, essential and pulmonary hypertension, renal disease, acute and chronic renal failure, end stage renal disease, peripheral vascular disease, male erectile dysfunction, diabetic retinopathy, 15 intermittent claudication/ischemic limb disease, ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis, pulmonary fibrosis, sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders, 20 Alzheimers disease, impulsivity, anxiety, stress, depression, parkinsons, movement disorders, sleep-wake cycle, incentive motivation, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/14409

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/41; C07D 207/08; A61P 9/00
US CL : 514/444; 548/518, 527

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/444; 548/518, 527

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
STN-CAS ONLINE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/38845 A1 (TULARIK INC.) 5 August 1999 (05.08.1999), abstract and examples.	1-7
A	WO 98/27081 A1 (SMITHKLINE BEECHAM PLC) 25 June 1998 (25.06.1998), claims 1-16.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	
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"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

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